Policy Subject: Hereditary Angioedema Agents
Policy Number: SHS PBD21
Category: Medical
Policy Type: Medical
Department: Pharmacy

Policy Statement:
Physicians Health Plan, PHP Insurance & Service Company, and Sparrow PHP will cover Hereditary angioedema agents through the Medical Benefit based on approval by the Clinical Pharmacist or Medical Director using the following determination guidelines.

Drugs and Applicable Coding:
J-code: Cinryze - J0598; Berinert - J0597, J1290; Kalbitor - J2425; Firazy - 014778; Ruconest - J0596
Takhzyro - pending

Clinical Determination Guidelines:
Document the following with chart notes:

A. Hereditary Angioedema (HAE)
   1. Age:
      a. Berinert IV (C1 Estrase Inhibitor Human), Cinryz IV (C1 Inhibitor Human), Ruconest IV (C1 esterase Inhibitor, recombinant), Haegarda SC (C1 Inhibitor Human): Adolescents and adults
      b. Firazy (icatiban): > 18 years
      c. Kalbitor (ecallantide): > 16 years
      d. Haegarda (C1 Inhibitor Human):
      e. Takhzyro (lanadelumab-flyo): >12 years
   2. Prescriber: Allergist, immunologist or hematologist
   3. Diagnosis and severity
      a. Lab test: both below
         • C4: <14mg/L (normal 9-36 mg/dL)
         • C1 Inhibitor (antigenic) <19.9mg/dL (normal 21-39mg/dL) or C1 Inhibitor (functional) <72% reference range (normal >67% reference range)
      b. Severity: Swelling of face/throat or GI tract that notably interferes with routine daily activities.
      c. Concomitant medications: Medications known to cause angioedema (ie. ACE inhibitors, estrogens, ARBs) have been evaluated and discontinued when appropriate
Pharmacy Benefit Determination Policy

B. Acute HAE treatment
1. Administration:
   a. Self-administration: Berinert, Firazyr and Ruconest after training by healthcare professional
   b. Healthcare professional administration: Kalbitor
2. Dosage regimen:
   a. Berinert IV (plasma-derived C1 INH): 20U/Kg
   b. Ruconest IV (recombinant C1 INH): < 84 Kg: 50 U/KG, > 84 Kg: 4,200 U; may repeat x 1
   c. Kalbitor SC (ecallantide): 30mg (3 x 1mL)
   d. Firazyr SC (icatibant): 30mg
3. Approval:
   a. Initial: 6 months;
   b. Re-approval: 1 year; quantity dependent on frequency of attacks (decreased severity and duration of attacks)

C. Prophylactic HAE treatment
1. Diagnosis and severity:
   a. Frequent and severe HAE attacks: > 24 days/year with symptoms or > 12 severe attacks/year.
   b. Severe HAE attacks in triggering situations: Major dental work, surgical procedures or invasive medical procedures
2. Other therapies: Failed or contraindication/significant adverse effects from 1 below:
   a. Acute HAE treatment (see B)
   b. Attenuated androgens: danazol, stanozolol
3. Dosage regimen
   a. Cinryz IV (C1 Inhibitor Human): 1,000U every 3-4 days
   b. Haegarda SC (C1 Inhibitor Human): 60U/Kg every 3-4 days
   c. Takhyro SC (lanadelumab-flyo): 300mg every 2 weeks
4. Approval
   a. Initial: 6 months
   b. Re-approval: 1 year (functional improvement with decreased frequency, severity and duration of attacks)
### Appendix I: Monitoring & Patient Safety

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Reactions</th>
<th>Monitoring</th>
<th>REMS</th>
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<tbody>
<tr>
<td>Berinert IV</td>
<td>• CNS: HA (17%) • GI: Nausea (18%) • Preg.: Animal reproductive studies have not been conducted</td>
<td>• CV: S &amp; Sx thrombolytic events • Immunologic: S &amp; Sx hypersensitivity.</td>
<td>Not needed</td>
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<tr>
<td>Cinryze IV</td>
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<td>Haegarda SC plasma C1-INH</td>
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<tr>
<td>Kalbitor</td>
<td>• CNS: HA (8-16%), fatigue (12%) • GI: Nausea (5-13%), diarrhea (4-11%) • Immunologic: Antibody development (IgE: 5-20%, neutralizing: 9%) • Preg.: Adverse effects were observed in animal studies</td>
<td>• Immunologic: S &amp; Sx hypersensitivity</td>
<td>REMS program Dc’ed by FDA April 2013</td>
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<td>Rascalitide</td>
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<td>Takhzyro SC</td>
<td>• CNS: HA (33%) • Immunologic: antibody development (12%) • Local: Injection site reaction (45-56%) • MSK: Myalgia (11%) • Resp: URI (44%)</td>
<td>• NA</td>
<td>Not needed</td>
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<td>lanadelumab-flyo</td>
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<tr>
<td>Firazyr SC</td>
<td>• Derm.: Inj. site Rx (97%), • Preg.: Adverse effects were observed in animal studies</td>
<td>• Symptoms relief laryngeal sx/airway obstruction</td>
<td>Not needed</td>
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<td>icatibant</td>
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<tr>
<td>Ruconest IV</td>
<td>• CNS: HA (&gt;10%) • GI: Abdominal pain (&gt;12%) • Resp.: Oropharyngeal (&gt;12%)</td>
<td>• CV: S &amp; Sx thrombolytic events • Misc: S &amp; Sx hypersensitivity</td>
<td>Not Needed</td>
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<tr>
<td>recombinant C1 INH</td>
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### References and Resources:

1. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Berinert, Cinryze, Haegarda; Firayz; Ruconest, Kalbitor, Takhzyro. accessed November 2018
10. Review of recent guidelines and consensus statements on hereditary angioedema therapy with focus on self-administration Int Arch Allergy Immunol. 2013;16(suppl 1):3-9
12. Hereditary angioedema: General and long-term prophylaxis. UpToDate. Waltham, MA: UpToDate Date Inc. accessed August 2017
### Approved By:

<table>
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<th>Name</th>
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<tr>
<td>Peter Graham, MD – PHP Executive Medical Director</td>
<td>10/25/17</td>
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<td>Human Resources – Kurt Batteen</td>
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